MedicalXpress

Two studies provide insight into stroke risk and prevention in young sickle cell anemia patients

December 6 2010

Monthly blood transfusions combined with daily medication to remove the resulting excess iron remains the best approach for reducing the risk of recurrent strokes in young patients with sickle cell anemia, according to a preliminary analysis of a multicenter trial that includes St. Jude Children's Research Hospital.

The study compared the efficacy of two treatments for the potentially life-threatening problem of iron overload caused by chronic transfusion therapy. The transfusions are used to guard against additional strokes in young sickle cell anemia patients. The trial, known as SWiTCH or Stroke with Transfusion Changing to Hydroxyurea, was halted in May after an interim safety review determined the alternative therapy was not significantly better than the standard treatment at reducing iron buildup and was associated with an increased stroke risk.

Russell Ware, M.D., Ph.D., chair of the St. Jude Children's Research Hospital Department of Hematology and principal investigator of SWiTCH, discussed the results at the 52nd Annual Meeting of the American Society of Hematology. The meeting is being held December 4 -7 in Orlando, Fla.

Jonathan Flanagan, Ph.D., a staff scientist at St. Jude, presented results of another study that provide the first independent validation of an association between five common genetic variations and stroke risk in

young sickle cell patients.

Between 70,000 and 100,000 individuals in the U.S. have sickle cell anemia. They make an abnormal hemoglobin molecule that sometimes takes on a twisted or sickle shape, disrupting blood flow and oxygen delivery throughout the body. Patients are vulnerable to a variety of problems, including organ damage, episodes of acute pain and stroke. Five to 10 percent of patients will suffer strokes before their 20th birthday. Up to 90 percent of patients will experience a recurrence.

Flanagan and his colleagues tried to validate earlier reports linking 38 genetic polymorphisms to stroke risk in sickle cell disease. Researchers compared the genetic makeup of 130 young sickle cell anemia (SCA) patients enrolled in the SWiTCH trial with 103 SCA patients enrolled in another study. The SWiTCH participants had suffered documented strokes while patients in the other trial had not.

Investigators validated the association between stroke risk and five single nucleotide polymorphisms (SNPs) in four genes. SNPs are small inherited variations in the makeup of particular genes and are sometimes used as markers of disease risk. "These findings reinforce earlier observations suggesting there is a genetic component to stroke risk in sickle cell anemia. We are now focusing on how these five SNPs might play a role in stroke development," said Flanagan, the poster's first author. Ware is the senior author.

Investigators also confirmed that the alpha-thalassemia trait is associated with a reduced stroke risk. Affected individuals carry two or three, rather than the usual four, genes for making one of the hemoglobin proteins needed to ferry oxygen throughout the body. Researchers reported no association between another inherited condition, G6PD deficiency, and strokes.

SWiTCH was a Phase III trial funded by the National Heart, Lung, and Blood Institute. Between October 2006 and April 2009, 133 children and adolescents ages 5 through 18 enrolled at one of 25 participating U.S. centers. All had a diagnosis of sickle cell anemia, had an average age of almost 13, had suffered at least one stroke and had undergone monthly blood transfusions for an average of seven years.

Sixty-six were randomly assigned to continue monthly transfusions and to take the drug deferasirox, or Exjade, daily to remove excess iron from their bodies. The remaining 67 patients were assigned to treatment with hydroxyurea daily for 30 months to reduce stroke risk and to undergo monthly blood removal to reduce iron buildup.

Monthly blood transfusions are 90 percent effective at preventing future strokes in sickle cell patients. But Ware said the resulting iron overload and other factors have fueled interest in alternative approaches to stroke prevention.

Hydroxyurea received U.S. Food and Drug Administration approval in 1998 for use in adults with SCA. The medication works by stimulating production of fetal hemoglobin, an alternative form of the molecule. A pilot study found the drug offered a possible alternative for managing stroke risk.

The SWiTCH study was halted after a review of data from 62 patients found no statistically significant difference in iron concentrations in the liver biopsies of the two treatment groups.

As expected, strokes were more common among patients receiving hydroxyurea than those who continued transfusion therapy. Seven of the 67 patients in the hydroxyurea group had another stroke. There were no additional strokes in the chronic transfusion patients.

Provided by St. Jude Children's Research Hospital